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Spiro Heterocyclic Compounds. V.[1] Synthesis of Spiro[homophthalimide-4,4′-(4′*H*-pyran)] Compounds

Teruhisa Fujimaki and Hirotaka Otomasu*

Hoshi College of Pharmacy, 2-4-41, Ebara, Shinagawa-ku, Tokyo, 142, Japan

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The reaction of 2-methylphthalonimide (**1**) with malononitrile gave 4-dicyanomethylene-2-methylhomophthalimide (**2**) in 95% yield.

The Michael reaction of **2** with compounds having an active methylene or methyl group (**3a**—**d**) afforded the corresponding spiro[2-methylhomophthalimide-4,4′-(4′*H*-pyran)] compounds (**4a**—**d**). In contrast, the reaction of **2** with other active methylene compounds (**3e**—**h**) afforded only the same product, spiro[2-methylhomophthalimide-4,1′-(3′-amino-2′-cyano-5′,6′-dihydro-5′-methyl-1′*H*-pyrano[2,3-*c*]isoquinolin-6′-one)] (**5**), which was found to be produced by the reaction of **2** with homophthalimide in quantitative yield. All the latter reactions can be regarded as the results of retrograde Michael reactions between the reactants **2** and active methylenes (**3e**—**h**).

By refluxing a methanol solution of **2** in the presence of a basic catalyst, the ring-trasformation product, methyl 1-dicyanomethyl-2-methyl-3-oxo-isoindoline-1-carboxylate (**8**) was obtained in 80% yield.

Keywords——Michael reaction; retrograde Michael reaction; active methylene compound; spiro[homophthalimide-4,4′-(4′*H*-pyran)] compounds; 4-dicyanomethylene-2-methylhomophthalimide; spiro[2-methylhomophthalimide-4,1′-(3′-amino-2′-cyano-5′,6′-dihydro-5′-methyl-1′*H*-pyrano[2,3-*c*]isoquinolin-6′-one)]; methyl 1-dicyanomethyl-2-methyl-3-oxo-isoindoline-1-carboxylate

In the previous papers of this series,[1,2] we reported the synthesis of spiro[oxindole-3,4′-(4′*H*-pyran)] compounds, for pharmacological evaluation, by the Michael reaction of 3-cyanomethyleneoxindole with an active methylene group. In this connection, we next attempted the synthesis of analogous pyran compounds with a spiro system at C-4 of homophthalimide.

The carbonyl group at C-4 of phthalonimide (**1**) is expected to have high reactivity, since the functional groups and their electron contributions are structurally related to those of indoline-2,3-dione. Using our procedure,[1,2] **1** was converted into the dicyanomethylene compound (**2**) and then to the title compounds. The details are presented in this paper.

2-Methylphthalonimide (**1**) was allowed to react with malononitrile under anhydrous conditions in the presence of piperidine as a catalyst at room temperature for 48 h, and a pale yellow solid (**2**) was obtained in excellent yield. The infrared (IR) spectrum showed the presence of two CN groups in the compound **2** as two weak peaks at 2220 and 3310 cm^{-1}. The fact that the IR absorption at 1700 cm^{-1} disappeared whereas those at 1710 and 1660 cm^{-1} (due to the C=O groups of homophthalimide) remained after this reaction indicated that the C=O absorption of 1700 cm^{-1} was ascribable to 4-C=O of the starting compound **1**. Therefore, the product **2** was concluded to be 4-dicyanomethylene-2-methylhomophthalimide.

Michael reactions against the α,β-unsaturated system of compound **2** were carried out. The reaction of **2** with an equimolar amount of an active methylene compound, such as acetylacetone (**3a**), ethyl acetoacetate (**3b**) or ethyl benzoylacetate (**3c**), in ethanol in the presence of piperidine as a catalyst at room temperature afforded the corresponding colorless product **4a**, **b** or **c**, respectively. Compound **2** reacted with methyl pyruvate (**3d**) as an active methyl group to give the homologous product **4d**. The results thus obtained are listed in Table I. All of the products **4a**—**d** showed the molecular ion peaks (M^+) corresponding to the normal Michael adducts in their mass (MS) spectra. The IR spectra of **4a**—**d** each showed a strong peak at 2200—2170 cm^{-1} characteristic of a conjugated CN group, and absorption bands

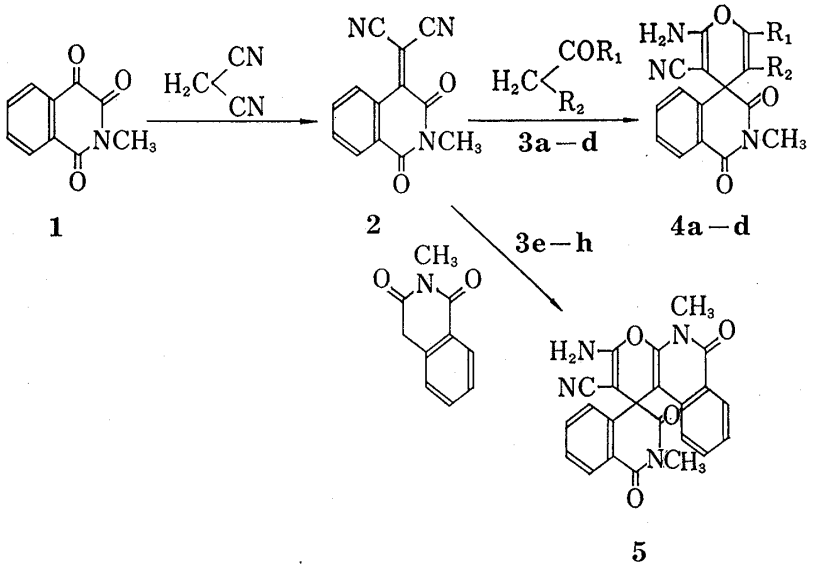
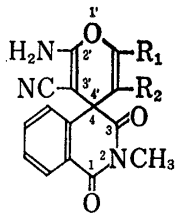


Chart 1

TABLE I. Spiro[homophthalimide-4,4′-(4′*H*-pyran)] Compounds



Compd. No.	R_1	R_2	Yield (%)	mp °C	Recryst solvent	Formula	Analysis (%) Calcd (Found) C	H	N
4a	CH_3	$COCH_3$	53	272	MeOH	$C_{18}H_{15}N_3O_4$	64.09 (63.62	4.48 4.45	12.46 12.05)
4b	CH_3	$COOC_2H_5$	97	191	C_6H_5	$C_{19}H_{17}N_3O_5$	62.12 (62.14	4.66 4.61	11.44 10.95)
4c	C_6H_6	$COOC_2H_5$	82	118	EtOH	$C_{24}H_{19}N_3O_5$	67.12 (66.96	4.46 5.03	9.79 9.43)
4d	$COOCH_3$	H	32	222	MeOH	$C_{17}H_{13}N_3O_5$	60.17 (60.35	3.86 3.67	12.39 11.89)

Compd. No.	IR (cm^{-1}) Nujol NH_2	CN	C=O groups	^{1}H-NMR ($CDCl_3$) δ in ppm, J in Hz
4a	3380, 3210	2200	1650, 1670, 1705	2.24 (3H, s, $-C\underline{H}_3$), 2.52 (3H, s, $-COC\underline{H}_3$), 3.24 (3H, s, $NC\underline{H}_3$), 7.33 (2H, s, $-N\underline{H}_2$), 7.27—8.08 (4H, m, Ar-$\underline{H}$)
4b	3410, 3310	2180	1650, 1675, 1700	0.80 (3H, t, J=7, $-C\underline{H}_3$), 2.49 (3H, s, $-C\underline{H}_3$), 3.42 (3H, s, $NC\underline{H}_3$), 3.80 (2H, q, J=7, $-C\underline{H}_2-$) 4.91 (2H, s, $-N\underline{H}_2$), 7.20—8.28 (4H, m, Ar-$\underline{H}$)
4c	3380, 3160	2180	1650, 1660, 1695	0.61 (3H, t, J=7, $-C\underline{H}_3$), 3.46 (3H, s, $NC\underline{H}_3$), 3.64 (2H, q, J=7, $-C\underline{H}_2-$), 5.10 (2H, s, $-N\underline{H}_2$), 7.45—8.28 (4H, m, Ar-$\underline{H}$)
4d	3420, 3320	2170	1640, 1660, 1720	3.40 (3H, s, $NC\underline{H}_3$), 3.82 (3H, s, $-C\underline{H}_3$), 5.29 (2H, s, $-N\underline{H}_2$), 7.43—8.28 (4H, m, Ar-$\underline{H}$)

due to NH_2 at 3400—3160 cm^{-1}. The presence of NH_2 in the molecules was also apparent in the proton magnetic resonance (PMR) spectra as a singlet (each 2H) at δ 7.33—4.91 which disappeared on the addition of D_2O. These spectral and analytical data were in good accord with the proposed spiro[2-methylhomophthalimide-4,4′-(2′-amino-3′-cyano-4′*H*-pyran)] structures **4a—d**.

However, in the reactions of **2** with other active methylene compounds as the Michael reagent, *e.g.*, benzoylacetone (**3e**), dibenzoylmethane (**3f**), cyanoacetamide (**3g**) and oxindole (**3h**), the results were entirely different, *viz.* all the latter reactions afforded the same colorless needles **5** as a common product, in the yields of about 10%. The MS of **5** showed M^+ at *m/e* 412 and its IR spectrum was very similar to those of the products **4a—d**. The PMR spectrum of **5** showed signals at δ 3.74 and 3.64 (each 3H, s) attributable to two NCH_3 protons and a singlet at 7.68 (2H, s) which disappeared on the addition of D_2O, and a multiplet at 8.23 —7.29 (8H) due to aromatic protons. From the above results along with the analytical data, the structure of the product **5** was designated as spiro[2-methylhomophthalimide-4,1′-(3′-amino-2′-cyano-5′,6′-dihydro-5′-methyl-1′*H*-pyrano[2,3-*c*]isoquinolin-6′-one)]. In view of the structure of **5**, it is likely that **5** is the product of reaction of **2** with the homophthalimide as

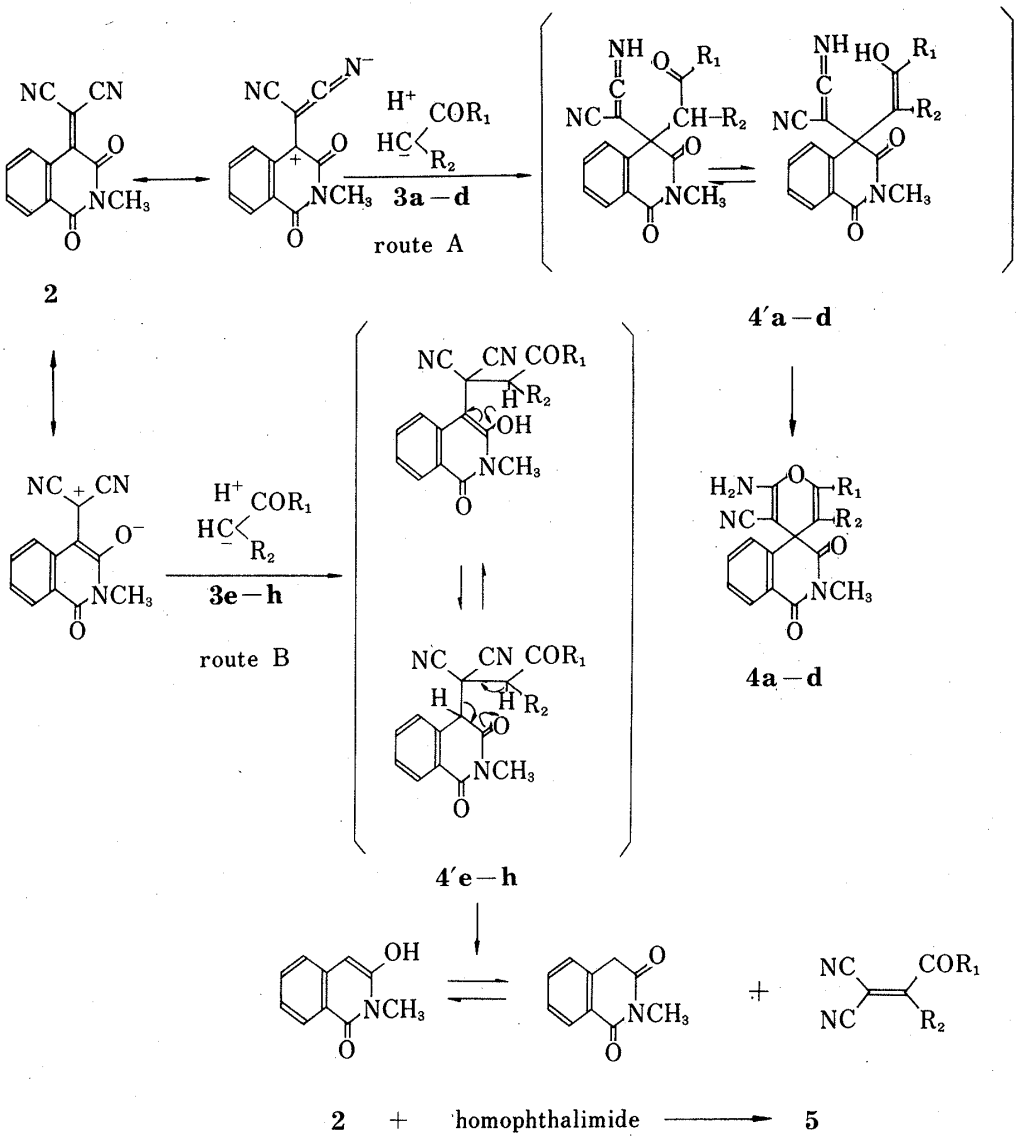


Chart 2

the Michael reagent. Thus, the reaction of **2** with homophthalimide under the same conditions was carried out and the product **5** was obtained in almost quantitative yield.

Consequently, formation of the compounds **3** and **5** from **2** may occur as shown in Chart 2. Thus, the attack of the carbanion of the active methylene group on the C-4 carbon of **2** produces the normal Michael adducts **4'a—d**, which enolized and then undergo cyclo-addition between the OH and CN groups to form the 2'-amino-4'*H*-pyran compounds **4a—d** (route A). The formation of **5** from **2** with homophthalimide is considered to occur in a similar manner. On the other hand, the formation of **5** from **2** with some other active methylene compounds (**3e—h**) can be regarded as being due to retrograde Michael reactions between the reactants **2** and **3e—h**. As shown in route B, the attack of the carbanion of the active methylene group on the exo-methylene carbon of **2** could form the Michael adducts **4'e—h**, which cleave to yield homophthalimide. It is known that the retrogression is more likely to occur when the reaction is slow.[3] Accordingly, the remaining **2** in the reaction mixture gave the compound **5** as a result of condensation with the released homophthalimide.

Finally, the condensations of **2** with amidines, which seemed to produce spiro[homophthalimide-4,4'-pyrimidine] compounds in a similar manner, were carried out. The reactions carried out in methanol did not give the corresponding product **6** but an unexpected product **8** having M^+ at *m/e* 269, which is 32 mass units (CH_3OH) greater than that of **2**. Since **8** was also obtained in 80% yield by refluxing **2** in methanol in the presence of piperidine as a catalyst, **8** was found to be merely a methanolysis product of **2**.

The PMR spectrum of **8** showed signals at δ 3.85 (3H, s) and 3.26 (3H, s), assigned to OCH_3 and NCH_3 protons, respectively, and at 4.98 (1H, s) due to a methine proton whose intensity decreased on D_2O treatment, as well as a multiplet (4H) of aromatic protons. The ^{13}C nuclear magnetic resonance (CMR) spectrum of **8** indicated the presence of one quaternary (δ 69.48), one methine (29.38), and two each of CN (111.15), C=O (116.17 and 167.14) and methyl carbons in the molecule, as well as six aromatic carbons. Further more, the MS of 8 revealed two fragmentation processes, *m/e* 268 (M^+)→210 ($M^+ - COOCH_3$) and M^+→204 ($M^+ - CH(CN)_2$), as shown in Chart 4. Two other plausible structures **9** and **10** for the methanolysis product of **2** were ruled out by the above MS data. The above results were all consistent

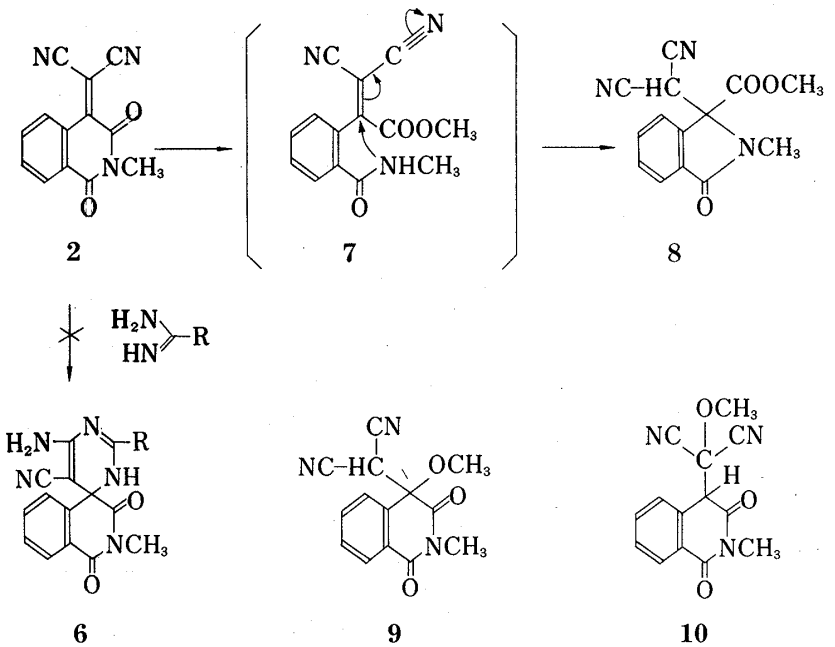


Chart 3

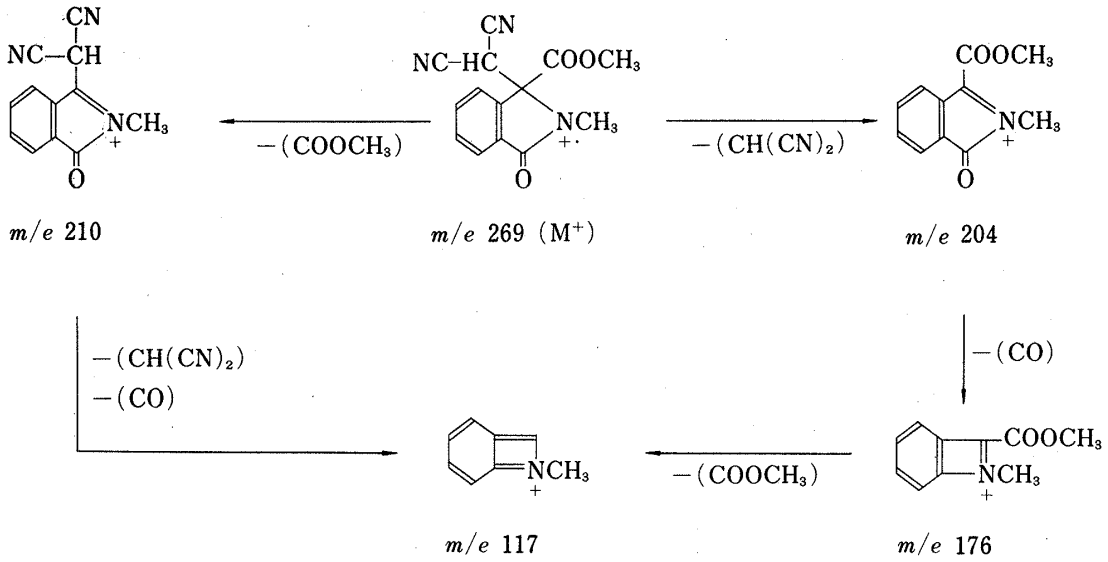


Chart 4

with the identification of the product **8** as methyl 1-dicyanomethyl-2-methyl-3-oxo-isoindoline-1-carboxylate.

This ring transformation can best be explained, as shown in Chart 3, by assuming the initial formation of a ring-opening intermediate (**7**) by the methanolysis of **2** followed by recyclization involving the attack of the methylamino anion on the strongly cationic benzylidene carbon to give the isoindoline skeleton.

Experimental

All melting points were determined in a capillary and are uncorrected. IR spectra were recorded with a Hitachi 215 machine and MS with a JEOL-D300 instrument at 70 eV. ^1H and ^{13}C NMR spectra were measured on a JEOL FX-100 (100 MHz) spectrometer using tetramethylsilane as an internal standard. Solutions were concentrated on a rotary evaporators *in vacuo*.

The starting material (**1**) was prepared according to the method of Buu-Hoi *et al.*[4]

4-Dicyanomethylene-2-methylhomophthalimide (2)——A solution of **1** (10.0 g) and malononitrile (5.23 g) in a mixed solvent of anhydrous benzene (100 ml) and absolute EtOH (100 ml) was treated with 5—6 drops of piperidine at room temperature with stirring. Stirring was continued for 48 h with moisture exclusion by means of a $CaCl_2$ tube, then yellowish solid that had separated was collected and rinsed with benzene. Yield, 11.5 g (95%). Recrystallization from anhyd. benzene gave yellow prisms of mp 206—208°C. IR ν_{max}^{Nujol} cm^{-1}: 2220 w (CN), 2210 w (CN), 1710 (3-C=O), 1660 (1-C=O). MS *m/e*: 237 (M^+). *Anal.* Calcd for $C_{13}H_7N_3O_2$: C, 65.82; H, 2.98; N, 17.12. Found: C, 65.45; H, 2.99; N, 17.56.

Reactions of 2 With an Active Methylene Group: Formation of Spiro[2-methylhomophthalimide-4,4′-(4′H-pyran)] Compounds (4a—d)——In a typical experiment, 3 drops of piperidine were added to a solution of **2** (2.0 g) and acetylacetone (0.85 g) in a mixed solvent of anhyd. benzene (30 ml) and absol. EtOH (30 ml) at room temperature with stirring. Stirring was continued for 18 h, then the solvent was removed. The product solidified on trituration in a small amount of CH_2Cl_2. Yield, 1.6 g (52.8%). Recrystallization from MeOH gave colorless prisms, mp 272°C (**4a**).

In a similar manner, the reactions of **2** with ethyl acetoacetate, ethyl benzoylacetate and methyl pyruvate gave the corresponding products (**4b—d**, respectively). In the case of the reaction with methyl pyruvate, methanol was used as the solvent. The results are summarized in Table I.

Spiro[2-methylhomophthalimide-4,4′-(3′-amino-2′-cyano-5′,6′-dihydro-5′-methyl-1′*H*-pyrano[2,3-*c*]-isoquinolin-6′-one)] (5)——i) In a typical run, 5 drops of piperidine were added to a solution of **2** (2.0 g) and benzoylacetone (1.4 g) in a mixed solvent of anhyd. benzene (50 ml) and absol. EtOH (50 ml), and the mixture was warmed at 40—50°C with sirring for 18 h. After the solvent had been removed, the residue was washed with MeOH and recrystallized from MeOH to give colorless granular crystals, mp 284°C. Yield, 0.15 g (8.6%). IR ν_{max}^{Nujol} cm^{-1}: 3350, 3170 (NH_2), 1715, 1675, 1660 (C=O). PMR (DMSO-d_6) δ: 3.34 (3H, s, NCH_3), 3.64 (3H, s, NCH_3), 7.68 (2H, s, NH_2), 7.29—8.23 (8H, m, Ar–H). MS *m/e*: 412 (M^+). *Anal.* Calcd for $C_{23}H_{16}N_4O_4$: C, 66.98; H, 3.91; N, 13.59. Found: C, 67.02; H, 3.71; N, 13.98.

In a similar manner, all of the reactions using dibenzoylmethane, cyanoacetamide and oxindole gave the same product **5** in about 10% yields.

ii) A solution of **2** (1.0 g) had homophthalimide (0.74 g) in a mixed solvent of anhyd. benzene (30 ml) and absol. EtOH (30 ml) was treated with 3 drops of piperidine and the mixture was warmed at 40—50°C with stirring for 18 h. The solvent was removed and the residue was recrystallized from MeOH to give colorless crystals of **5**. Yield, 1.7 g (98%).

Methyl 1-Dicyanomethyl-2-methyl-3-oxo-isoindoline-1-carboxylate (**8**)——i) A mixture of **2** (0.2 g), benzamidine HCl (0.17 g) and K_2CO_3 (0.21 g) in MeOH (30 ml) was refluxed for 1.5 h. After cooling, the mixture was filtered and the filtrate was concentrated to dryness. The resulting product was recrystallized from benzene to give colorless prisms of mp 142°C. Yield, 0.18 g (75%). IR ν_{max}^{Nujol} cm^{-1}: 1740 ($COOCH_3$), 1700 (C=O). PMR ($CDCl_3$) δ: 3.26 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 4.98 (1H, s, >CH–), 7.64—8.01 (4H, m, Ar–H). CMR ($CDCl_3$) δ: 29.38 (d, >CH–), 69.49 (s, quaternary carbon), 111.15 (s, 2 CN), 166.17 (s, C=O), 167.14 (s, C=O). MS *m/e*: 269 (M^+, 18%), 210 ($M^+-COOCH_3$, 100), 203 ($M^+-CH(CN)_2$, 80), 176 (34), 117 (30). *Anal.* Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.04; H, 3.74; N, 15.45.

ii) Methanolysis of **2**. A solution of **2** (2.0 g) in a mixed solvent of anhyd. benzene (40 ml) and MeOH (40 ml) was treated with 4 drops of piperidine and the mixture was refluxed for 1.5 h. The reaction mixture was treated in the manner described above, and the same product (**8**) was obtained in 80% yield.

References and Notes

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3) E.D. Bergmann, D. Ginsburg, and R. Pappo, "Organic Reactions," Vol. 10, John Wiley & Sons, Inc. p. 187.
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